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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
VIVLEMORE, TRACY ANN	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 03/02/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/045,992	LINDNER ET AL.	
	Examiner	Art Unit	
	Tracy Vivlemore	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 December 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-55* is/are pending in the application.

4a) Of the above claim(s) *1-22 and 25-55* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *23 and 24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 112

The rejection of record of claims 23 and 24 under 35 USC 112, second paragraph and 35 USC 112, first paragraph for lack of written description, is withdrawn in view of the amendment of December 17, 2004.

Claims 23 and 24 are maintained as rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The following factors as enumerated *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), are considered when making a determination that a disclosure is not enabling: the breadth of the claims, the nature of the invention, the state of the prior art, the level of ordinary skill in the art, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples and the quantity of experimentation needed to make the invention based on the content of the disclosure.

1. Claim 23 is drawn to a method of treating a disease in a human using an isolated nucleic acid molecule complementary to SEQ ID NO: 3. Claim 24 designates the treated disease as being hypertrophic scar formation. Methods of gene therapy directed toward inhibition of gene expression in humans are not enabled because of the unpredictability in the art.

2. The state of the art prior art is such that inhibition of gene expression *in vitro* is routine, but *in vivo* inhibition of gene expression at the time of filing and even to the present time is not routine for several reasons, including the problems of delivery, specificity and duration.

3. The specification describes on pages 130-133 the identification and isolation of rat REMODELIN from injured arterial walls and identification of human REMODELIN from sequence homology searching. The specification contemplates using antisense oligonucleotides to inhibit expression of REMODELIN on pages 61-64, contemplates putting antisense oligonucleotides in a vector for the purposes of elucidating mechanisms of action of REMODELIN on pages 72-73 and on pages 108-110 contemplates using antisense oligonucleotides to decrease REMODELIN expression in order to treat a disease condition associated with increased REMODELIN expression.

4. The only disclosed example using antisense sequences to REMODELIN is on page 141, where suppression of REMODELIN expression in MC3T3 cells using a vector containing an antisense to rat REMODELIN is described. On pages 91-104 the specification provides general statements regarding physical forms that a therapeutic composition might have and general methods of delivery. However, there is no specific

guidance on how to administer such oligonucleotides to a human in such a manner that the oligonucleotide would reach the affected cells in a form and in an amount such that detectable and significant inhibition of REMODELIN expression would occur in order to alleviate a disease state.

5. The problems of nucleic acid based therapies and antisense technology are well known in the art, particularly with regard to the inability to specifically deliver an effective concentration of a nucleic acid to a target cell, such that a target gene is inhibited to a degree necessary to result in a therapeutic effect. For example, at the time the instant invention was made, the therapeutic use of nucleic acids was a highly unpredictable art due to obstacles that continue to hinder the therapeutic application of nucleic acids *in vivo* (whole organism) (see for example Agrawal et al. (Molecular Medicine Today, 2000, vol 6, p 72-81), Branch (TIBS 1998, vol. 23, p. 45-50) and Jen et al. (Stem Cells 2000, Vol. 18, p 307-319)). Such obstacles include, for example, problems with delivery, target accessibility and the potential for unpredictable nonspecific effects.

6. The instant specification discloses the method can be performed by administration of an antisense oligonucleotide via delivery methods including oral, intraocular and topical. None of these delivery methods was routine in the art at the time of filing. Jen et al. state (see page 313, second column, second paragraph) "One of the major limitations for the therapeutic use of AS-ODNS and ribozymes is the problem of delivery....presently, some success has been achieved in tissue culture, but efficient delivery for *in vivo* animal studies remains questionable". Jen et al. outlines many of the factors limiting the application of antisense for therapeutic purposes and

concludes (see p 315, second column), "Given the state of the art, it is perhaps not surprising that effective and efficient clinical translation of the antisense strategy has proven elusive."

7. Opalinska et al. (Nature Review, 2002, vol 1, p. 503-514) state "[I]t is widely appreciated that the ability of nucleic-acid molecules to modify gene expression *in vivo* is quite variable, and therefore wanting in terms of reliability. Several issues have been implicated as a root cause of this problem, including molecule delivery to targeted cells and specific compartments within cells and identification of sequence that is accessible to hybridization in the genomic DNA or RNA" and in column 2 of the same page, "Another problem in this field is the limited ability to deliver nucleic acids into cells and have them reach their target. Without this ability, it is clear that even an appropriately targeted sequence is not likely to be efficient. As a general rule, oligonucleotides are taken up primarily through a combination of adsorptive and fluid-phase endocytosis. After internalization, confocal and electron microscopy studies have indicated that the bulk of the oligonucleotides enter the endosome-lysosome compartment, in which most of the material becomes either trapped or degraded."

8. Given this unpredictability, the skilled artisan would require specific guidance to practice the claimed methods *in vivo* in humans, with a resultant inhibition of gene expression, as claimed. The specification provides one example of delivery of an antisense oligonucleotide to mouse cells *ex vivo*, however, cell culture examples are generally not predictive of *in vivo* inhibition and the methods of delivery of the exemplified cell line would not be applicable to delivery of oligonucleotides to any

organism. Often formulations and techniques for delivery *in vitro* (cell culture) are not applicable *in vivo* (whole organism) (see for example Jen et al., page 313, second column, second paragraph). For example, Agrawal et al. (see p 79-80, section entitled "Cellular uptake facilitators for *in vitro* studies") states "The cellular uptake of negatively charged oligonucleotides is one of the important factors in determining the efficacy of antisense oligonucleotides.....*In vitro*, cellular uptake of antisense oligonucleotides depends on many factors, including cell type, kinetics of uptake, tissue culture conditions, and chemical nature, length and sequence of the oligonucleotide. Any one of these factors can influence the biological activity of an antisense oligonucleotide." Due to differences in the physiological conditions of a cell *in vitro* versus *in vivo*, the uptake and biological activity observed *in vitro* would not predictably translate to *in vivo* results.

9. Given these teachings, the skilled artisan would not know *a priori* whether introduction of antisense oligonucleotides to humans by the broadly disclosed methodologies of the instant invention, would result in successful inhibition of expression of the target gene. One of skill in the art would not know how to deliver oligonucleotides to a human in such a way that would ensure an amount sufficient to modify or inhibit expression of a target gene is delivered to the proper cell.

10. In fact, the state of the art is such that successful delivery of oligonucleotide sequences *in vivo* or *in vitro*, such that the polynucleotide or oligonucleotide provides the requisite biological effect to the target cells/tissues/organs, must be determined empirically. Methods of inhibiting gene expression using nucleic acids *in vivo* are

unpredictable with respect to delivery of the nucleic acid molecule such that the nucleic acid molecule is targeted to the appropriate cell/organ, at a bioeffective concentration and for a period of time such that the nucleic acid molecule is effective in, as in the instant application, attenuating or inhibiting expression of a target gene such that the organism exhibits a therapeutic response to a disease.

11. The specification teaches the use of an antisense vector to suppress expression of REMODELIN in one mouse cell line but does not provide the guidance required to overcome the art-recognized unpredictability of using antisense oligonucleotides in therapeutic applications in any organism, including humans. The field of antisense therapeutics does not provide that guidance, such that the skilled artisan would be able to practice the claimed therapeutic methods. The specification does not provide any specific guidance for overcoming the known unpredictable factors regarding the successful *in vivo* application of antisense.

12. Thus, while the specification is enabling for the delivery of an antisense oligonucleotide to mouse cells *ex vivo* as set forth in the specification, the specification is not enabling for the broad claim of treating a disease associated with an abnormal expression of REMODELIN in a human as the art of inhibiting gene expression by introducing antisense oligonucleotides into an organism is neither routine nor predictable. In order to practice the claimed invention *in vivo* a number of variables would have to be optimized, including 1). the mode of delivery of the oligonucleotide to an organism that would allow it to reach the targeted cell, 2). the amount of oligonucleotide that would need to be delivered in order to allow inhibition of the

expression of a target gene once it reached the proper cell and 3). ensuring the oligonucleotide remains viable in a cell for a period of time that allows inhibition of the gene to an extent that there is a measurable and significant therapeutic effect. Each one of these variables would have to be empirically determined for each antisense oligonucleotide. While optimization of any single one of these steps may be routine, when taken together the amount of experimentation becomes such that one of skill in the art could not practice the invention commensurate in scope with the claims without undue, trial and error experimentation and therefore, claims 23 and 24 are not enabled.

Response to Arguments

13. Applicant's arguments filed December 17, 2004 have been fully considered but they are not persuasive. The amendment to the claims overcomes the written description rejection and thus reduces the amount of experimentation necessary to practice the invention as claimed. However, neither the specification as filed nor the amendment overcomes the art-recognized unpredictability of nucleic acid therapeutics in terms of delivery, specificity and duration.

14. Applicant argues that the references used to demonstrate how the claimed methods are not enabled in fact provide a survey of the experimentation needed to perform the claimed methods.

15. This argument is not persuasive. The type of experimentation required to practice the invention more broadly than it is exemplified is a factor in the enablement analysis but it is not dispositive. In this case, the more-or-less standard nature of each

type of experiment required to expand the scope of the enabled invention is outweighed by the sheer quantity of experimentation required to practice the full scope of the claims, the unpredictability of the art generally and the claimed method in particular and the lack of guidance in the specification regarding the direction in which the experimentation should proceed.

16. Applicant argues that Opalinska et al. state delivery problems are "easily solved". In fact, these two words are taken out of context. This phrase was in no way referring to generalized problems with delivery of nucleic acid therapeutics being easily solved but instead described how a side effect resulting from one type delivery method was avoided. Delivery is more than simple administration: injection of an antisense into the bloodstream of an animal does not guarantee that the drug will enter a cell, nor does it guarantee the drug will reach the cell that is diseased, specificity (for the cell, not the target) is a concern as well. Cellular uptake is an important question, as stated by Agrawal.

17. Applicant argues that accessibility is not a problem since Jen refers to the targeting of mRNA being attractive because it is "more accessible than the corresponding gene". However, Jen is comparing the accessibility of mRNAs in general, which are located in the cytoplasm of a cell during translation, versus the accessibility of genes, which are located exclusively within the nucleus of a cell. This statement was not referring to delivery of a nucleic acid into a cell. Applicant also refers to page 313, second column of Jen, which describes various delivery methods and asserts this shows that experimentation with regard to delivery is routine. This is the

same paragraph cited in the examiner's rejection and the first and last sentences are particularly pertinent to the question of enablement: "One of the major limitations for the therapeutic use of AS-ONs and ribozymes is the problem of delivery" and "Presently, some success has been achieved in tissue culture, but efficient delivery for in vivo animal studies remains questionable". This paragraph does not show that experimentation with regard to delivery is routine but in fact demonstrates that numerous routes have been tried and none have proved to be work dependably.

18. Applicant argues that Agrawal provides a significant amount of guidance in the optimal design of antisense. This is true, general guidelines of modifications that have been successful are provided, but this guidance does not provide evidence that delivery of antisense targeted to a particular gene to a cell expressing this gene in an abnormal fashion works in a reliable manner. It also does not provide guidance of how much of an antisense needs to be delivered to the cell to ensure that it has a therapeutic effect. Additionally, Agrawal also describes how numerous factors can combine to affect the efficacy of any antisense oligonucleotide, cited in the examiner's rejection.

19. Applicant cites the clinical studies listed by both Agrawal and Opalinska as evidence that experimentation is routine in the art of nucleic acid therapeutics. However, the existence of a clinical trial involving an antisense drug does not demonstrate that the field of nucleic acid therapeutics is predictable. Further, these clinical trials do not involve antisense to REMODELIN nor are they directed to conditions associated with abnormal expression of REMODELIN.

20. Applicant asserts that the examiner has ignored the existence of an FDA approved antisense drug and the FDA's approval of this drug indicates the general applicability of antisense therapeutics and intraocular delivery. However, Vitravene is approved for use via intraocular delivery because it treats a disease associated with the eye. The approval of Vitravene is not a general statement that intraocular administration would be effective to deliver an antisense nucleic acid to a different part of the body and does not address how delivery of an antisense to REMODELIN to the eye would treat a disease not involved with the eye. If the antisense of the instant application were intended to treat ocular diseases, this might provide evidence of enablement of the instant claims. The approval of Vitravene also does not address the predictability of other delivery methods contemplated in the specification. Additionally, the existence of a single drug does not speak to the general applicability of antisense therapeutics. FDA approval of a drug to treat heart disease does not mean that all drugs that treat heart disease are automatically approved.

21. The important issues related to enablement of antisense therapeutics are these: Delivery is more than simple administration: injection of an antisense into the bloodstream of an animal does not guarantee that the drug will reach and enter the cell. Cellular uptake is an important question, as stated by Agrawal. Without a predictable delivery method it is impossible to know how much to administer. If injection will result in the drug dispersal throughout the circulatory system, how much will reach the actual diseased cell? In order to have a therapeutic effect, a drug has to get into the diseased

cell in a sufficient concentration and remain viable for a sufficient length of time to affect the expression of the target gene.

Conclusion

22. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tracy Vivlemore whose telephone number is 571-272-2914. The examiner can normally be reached on Mon-Fri 8:45-5:15.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached on 571-272-0760. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

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Tracy Vivlemore
Examiner
Art Unit 1635

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February 16, 2005